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(54) Title: TAXANE COMPOSITION AND METHOD

(57) Abstract

The invention provides a taxane storage solution having improved solubility and toxicity properties. The solution comprises a taxane, such as taxol or docataxel, in a pharmaceutically pure form, a polyoxyethylene sorbitan fatty acid monoester, polyethoxylated castor oil, and ethanol. The polysorbitan and polyethoxylated castor oil are present in amounts effective to reduce the toxicity of the taxane relative to the toxicity observed when either the polysorbitan or polyethoxylated castor oil is used in the absence of the other. Also disclosed is a therapeutic method which employs the solution, and a vehicle which may be used in the method.

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# TAXANE COMPOSITION AND METHOD

## Field of the Inventi n

The present invention relates to formulations of taxol and related taxane compounds, which have improved safety, solubility and stability characteristics, and to methods of preparing such formulations.

## References

Arbuck, S.G., and Blaylock, B.A., in TAXOL: SCIENCE AND APPLICATIONS, (Suffness, M., Ed.) CRC Press, New York, NY, pp. 379-415 (1995).

Straubinger, R.M., in TAXOL: SCIENCE AND APPLICATIONS, (Suffness, M., Ed.) CRC Press, New York, NY, pp. 237-258 (1995).

## Background of the Invention

Taxol, also known as paclitaxel, is a compound extracted from the bark of the western yew, *Taxus brevifolia*. Much attention has been drawn to taxol for use as an antineoplastic agent. Taxol has shown good response rates in the treatment of ovarian and breast cancer patients who did not respond to cisplatin or vinca alkaloid therapy. Taxol is also being examined for treating a variety of other cancers, such as melanoma, lymphoma and lung cancer.

A major problem associated with taxol is its low solubility in aqueous solvents. Because taxol lacks functional groups that are ionizable in a pharmaceutically acceptable range, manipulation of pH does not enhance solubility. Producing salts or adding charged complexing agents are also inapplicable (Straubinger, 1995, p. 238). Formulating taxol in a biocompatible carrier has thus been a challenge throughout its therapeutic development.

In the search for taxol formulations having improved solubility and toxicity properties, a number of pharmaceutical vehicles have been investigated. Generally, such vehicles have included a cosolvent, such as ethanol, dimethylsulfoxide (DMSO) or low molecular weight polyethylene glycol (*e.g.*, PEG 400), with or without an oil or surfactant additive such as a polyoxyethylene sorbitan fatty acid ester (*e.g.*, "TWEEN 80", also known as polysorbate-80), polyethoxylated castor oil (*e.g.*, "CREMOPHOR EL"), soybean oil, or triacetin. However, these formulations have suffered from either poor solubility, particularly following dilution into saline solution for intravenous administration, or from high toxicity, due to the oil or surfactant. In particular, the administration of "TWEEN-80" in amounts necessary to solubilize taxol at high concentration is associated with pleural effusions and edema, and "CREMOPHOR EL" can produce serious or fatal hypersensitivity (Straubinger, 1995, pp. 241 and 244).

There is therefore a need for formulations of taxol having reduced toxicity while maintaining high stability for long term storage.

## Summary of the Invention

The present invention includes, in one aspect, a taxane storage solution for pharmaceutical use. The storage solution comprises (a) a taxane compound in a pharmaceutically pure form, (b) a polyoxyethylene sorbitan fatty acid monoester, (c) polyethoxylated castor oil, and (d) ethanol. In the solution, the monoester and polyethoxylated castor oil are present together in amounts effective to reduce the toxicity of the solution relative to the toxicity observed when either the polyoxyethylene sorbitan fatty acid monoester or polyethoxylated castor oil is used in the absence of the other. The pH of the storage solution is preferably between about 1 and 8. The taxane compound is preferably taxol or docetaxel.

In a preferred embodiment, the solution additionally includes a low molecular weight polyethylene glycol, such as PEG 300.

The solution may additionally include a pharmaceutically acceptable acid as a buffering agent, wherein the pH is maintained between about 4 and about 6.

In a preferred embodiment, the storage solution includes 4 mg/mL to 8 mg/mL of a taxane, such as taxol, 20 to 30% (v:v) polyethoxylated castor oil, 5 to 15% (v:v) polyoxyethylene (20) sorbitan mono-oleate, 15 to 30% (v:v) ethanol, and 40 to 60% (v:v) low molecular weight polyethylene glycol.

In another aspect, the invention includes a method of treating a cancer condition in a mammalian subject. In the method, there is provided a taxane storage solution in accordance with the description above. The storage solution is diluted with a diluent suitable for intravenous administration, to produce a dilute taxane solution. The solution is then administered to the subject in a pharmaceutically acceptable amount effective to inhibit cancer growth in the subject. In preferred embodiments, the method is used to treat ovarian cancer or breast cancer.

The invention also includes a method of preparing a taxane solution for intravenous administration. In the method, a taxane storage solution of the type described above is diluted with a diluent suitable for intravenous administration, to produce a dilute taxane solution. The dilute taxane solution may be administered in a method of treating cancer, as noted above.

In another aspect, the invention includes a pharmaceutical vehicle for delivering a non-polar drug, such as taxol, to a subject. The vehicle includes a polyoxyethylene sorbitan fatty acid monoester, and polyethoxylated castor oil. The monoester and polyethoxylated castor oil are present in amounts effective to reduce the toxicity of the vehicle relative to the toxicity

observed when either the monoester or the polyethoxylated castor oil is used in the absence of the other. The vehicle is useful when a solubilizing agent is necessary to dissolve a non-polar drug in solution, and where using the polyoxyethylene sorbitan fatty acid monoester without the polyethoxylated castor oil, or oil without the monoester, produces toxic effects which limit the amount of drug that can be administered. In a preferred embodiment, the vehicle additionally includes a low molecular weight polyethylene glycol, such as PEG 300. The invention also includes a drug composition comprising a non-polar drug in a vehicle of the type just described.

These and other objects and features of the invention are described more fully below.

## Detailed Description of the Invention

### I. Definitions

As used herein, the terms below are intended to have the following meanings.

By "taxane" is meant any compound (a) having the 6-8-6 fused ring backbone of taxol, including additional substituents or bonding necessary for taxol activity (e.g., 9-ketone or 9-hydroxyl, 4,5-oxetane ring, 4-acetoxy, and 2-benzoyloxy; see also Chapter 13 on taxane structure-activity relationships in TAXOL: SCIENCE AND APPLICATIONS, cited above, particularly page 339), and (b) which inhibits depolymerization of microtubules. Exemplary taxane compounds are taxol (paclitaxel) and docataxel ("TAXOTERE").

By "polyoxyethylene sorbitan fatty acid monoester" is meant a compound having a sorbitan core (1,4-sorbitol cyclic ether), wherein the 2, 3, and 5-hydroxyl groups of the sorbitan core are each derivatized with one or more ethylene oxide monomers, and the 6-hydroxyl of the core is derivatized with one or more ethylene oxide monomers which terminate with a fatty acid ester group. The number of ethylene oxide monomers in the compound will generally be between 10 and 50, and preferably between 10 and 30. An exemplary polyoxyethylene sorbitan fatty acid monoester is "TWEEN 80", also known as polyoxyethylene (20) sorbitan mono-oleate, wherein "(20)" indicates that the total number of ethylene oxide monomers attached to the sorbitan core is 20.

By "fatty acid" is meant a C-16 to C-22 carboxylic acid which may be entirely aliphatic or may contain one or more carbon-carbon double bonds. Exemplary fatty acids include palmitic acid (C-16), stearic acid (C-18), and oleic acid (cis-9-octadecenoic acid).

By a polyoxyethylene sorbitan fatty acid monoester and polyethoxylated castor oil being "present together in amounts effective to reduce the toxicity of the solution relative to the toxicity observed when either the polyoxyethylene sorbitan fatty acid monoester or polyethoxyl-

ated castor oil is used in the absence of the other" is meant that the monoester and oil are present together in amounts effective to reduce the toxicity of a taxane storage solution (after dilution for intravenous administration) relative to the toxicity that would be obtained if the monoester/oil combination of the invention were replaced with monoester compound alone or oil compound alone in an amount sufficient to achieve the same degree of solubilization of the taxane compound as achieved by the monoester/oil combination.

By "low molecular weight polyethylene glycol" is meant polyethylene glycol (PEG) having an average molecular weight of 200 to 3000 daltons.

"Mammalian subject" is intended to have its traditional meaning, and encompasses cats, dogs, sheep, horses, and particularly humans, for example.

II. Taxane Storage Solution

The present invention is directed to an improved composition and method for delivering high doses of taxanes to cancer patients using a vehicle with reduced toxicity. The invention is based in part on the discovery that using a polyoxyethylene sorbitan fatty acid monoester in combination with a polyethoxylated castor oil, as solubilizing agents for a taxane compound, is effective to provide high taxol solubility and stability, but with reduced toxicity.

The storage solution of the invention includes a taxane in pharmaceutically pure form, which is solubilized at high concentration using a polyoxyethylene sorbitan fatty acid monoester and polyethoxylated castor oil in an ethanol base. Preferably, the taxane is present at a concentration of between about 2 and about 20 mg/mL, and typically between about 4 and about 8 mg/mL.

The monoester and polyethoxylated castor oil are present together in amounts effective to reduce the toxicity of the solution relative to the toxicity observed when either the polyoxyethylene sorbitan fatty acid monoester or the polyethoxylated castor oil is used in the absence of the other. The polyethoxylated castor oil is from any pharmaceutically acceptable source. One suitable preparation is available from BASF (Wyandotte, MD) under the trademark "CREMOPHOR EL". Generally, the polyethoxylated castor oil is present at a concentration of about 10 to about 40% (v:v), and preferably between about 20 to about 30%.

The sorbitan fatty acid monoester is generally present at a concentration of about 5 to about 20% (v:v), preferably between about 5 and about 15%. One preferred polyoxyethylene sorbitan fatty acid monoester is "TWEEN 80".

The polyethoxylated castor oil and sorbitan fatty acid monoester together constitute a total concentration in the storage solution of between about 15 to about 60%, preferably from

about 25 to 45% (v:v). In addition, the polyethoxylated castor oil and sorbitan monoester are used in a ratio (oil:sorbitan monoester, v:v) of between about 0.5 to 6, preferably between about 1.3 and 6, and more preferably between about 2 and 3. It should be noted that the polyethoxylated castor oil and polyoxyethylene sorbitan fatty acid monoester serve not only to enhance the solubility of the taxane, but also to enhance the anti-cancer potency of the taxane when administered against tumor cells. According to an important feature of the invention, using the polyethoxylated castor oil and sorbitan monoester together results in lower toxicity due to these components than would be expected if the oil is used without the monoester compound or the monoester compound is used without the oil compound.

The storage solution of the invention may also include a low molecular weight polyethylene glycol (PEG) having an average molecular weight of 200 to about 3000 daltons, preferably between about 200 and about 1000 daltons. The PEG preparation is preferably one which is a liquid at a temperature above 15°C, *e.g.*, having an average molecular weight of between about 200 and about 1000 daltons, and preferably between about 200 and about 500. PEG is optionally also included in the storage solution to improve the solubility and stability of the taxane. Preferably, the level of PEG is between 10 and 60%, more preferably between about 40 and about 60%.

The storage solution may also optionally include a buffering agent which maintains the pH of the storage solution between about 1 and about 8, preferably between about 4 and about 6. Preferably, the buffering agent is pharmaceutically acceptable acid, more preferably a carboxylic acid, such as citric acid, acetic acid, maleic acid, succinic acid, lactic acid, ascorbic acid, glutamic acid, or aspartic acid. Preferably, the buffering agent is anhydrous citric acid. The buffering agent may be present at a concentration of between about 2 and about 200 mM, typically between about 5 and about 20 mM. The remainder of the storage solution is preferably made up by ethanol. The storage solution preferably does not contain water.

The storage solution of the invention is prepared by any method suitable to solubilize the taxane component, including the use of sonication and heating. Exemplary methods for preparing solutions in accordance with the invention are provided in Example 1. The solution may be stored at room temperature, and preferably at 4°C or lower. The solution is preferably treated to remove particulate matter by passage through a filter membrane, *e.g.*, a 0.22 $\mu$m pore-size membrane. The solution may also be purged with nitrogen gas to remove oxygen.

The stability properties of the storage solution of the invention are illustrated by the studies described in Examples 2 and 3. In the study described in Example 2, aliquots of two storage solutions in accordance with the invention were placed in an autoclave and heated under

pressure at 250°C for 20 minutes. The samples were then diluted in acetonitrile and analyzed by HPLC. No sign of taxol degradation was detected.

In the study described in Example 3, sample solutions were incubated at 37°C for 12 weeks, and aliquots were periodically removed and tested by HPLC for degradation of taxol. The sample solutions tested included Formulations 1 and 2 from Example 1, as well as a solution containing taxol in a 1:1 mixture of polyethoxylated castor oil and ethanol (Formulation 3). As can be seen from the results in Example 3, the taxol solutions in accordance with the present invention are at least as stable as Formulation 3, with less than 2% degradation after 12 weeks.

According to another important feature of the invention, the storage solution of the invention is compatible with dilution into standard solutions for intravenous administration of drugs. In the study described in Example 4, the formulations from Example 1 were diluted in normal saline (0.9% NaCl in water) by dilution factors of 1:5, 1:10, 1:25 and 1:50 and were then examined for signs of precipitation or cloudiness after 1, 2, 4, 8, 24, and 48 hours. All dilutions remained clear for the first 24 hours for both formulations, and Formulation 1 remained clear for 48 hours. These results indicate that storage solutions in accordance with the invention are suitable for intravenous administration.

In the study described in Example 5, the relative toxicities of the storage vehicle alone (storage solution without taxol) were compared with a vehicle consisting of a 1:1 mixture of polyethoxylated castor oil and ethanol (Formulation 3). In one experiment, groups of 2 or 3 mice were administered single dosages of test formulations in undiluted form, and the mice were monitored for 21 days for signs of intolerance of the administered dosages. Signs of intolerance included any of the following: (1) significant weight loss (>20%), (2) piloerection, (3) prolonged prostration, and (4) death. The highest dosage volumes (MTD, maximum tolerated dose) which could be administered without causing signs of intolerance were recorded. As can be seen from the results in Example 5A, the maximum tolerated dose for formulations in accordance with the present invention is twice that of the formulation which used polyethoxylated castor oil alone, without sorbitan monoester.

Similar results are obtained when the same formulations are administered in small volumes/doses at 6 hour intervals for 5 days. Again, the maximum tolerated cumulative dose of formulations in accordance with the present invention is found to be twice that of the formulation using polyethoxylated castor oil alone. These results show that the vehicle of the present invention has lower inherent toxicity than when polyethoxylated castor oil is used without sorbitan monoester, allowing greater quantities of taxane to be administered, or alternatively,

the same amount of taxane as used before, but with reduced toxic side effects. The invention therefore provides a significant advantage over prior taxane formulations in which deleterious side effects of the vehicle itself have limited the amount of taxane which could be administered.

III. Treatment Method

In another aspect, the invention includes a method of treating a cancer condition in a mammalian subject. In the method, there is provided a taxane storage solution in accordance with the description above. The storage solution is diluted with a diluent suitable for intravenous administration, to produce a dilute taxane solution. The solution is then administered to the subject in a pharmaceutically acceptable amount effective to inhibit cancer growth in the subject.

The dilute taxane solution is administered to treat any cancer condition in which the taxane is effective to inhibit or destroy cancer growth. Such cancer conditions may include ovarian cancer, breast cancer, bladder cancer, lung cancer, melanoma, and lymphoma, for example.

The diluent used in the method is any intravenous solution suitable for intravenous administration. Typically, the diluent will include sodium chloride to establish a selected physiological osmolality, *e.g.*, 0.9% (w/v) sodium chloride). The diluent may additionally include suitable supplements, such as glucose, and/or an antimicrobial agent such as penicillin or tetracycline. The solution is preferably dispensed using a non-plasticized container, to prevent leaching of placticizers into the solution. The diluted taxane formulation is administered at a selected rate until the desired amount of drug has been administered. The formulation is administered periodically until remission has been achieved, or until it appears that proliferation of the target cancer is inhibited. The formulation may also be administered following surgery to inhibit recurrence of the cancer, for a time sufficient to indicate that the cancer has been successfully removed.

Dosage regimens for treating cancer patients with taxol and taxol derivatives are known in the art and are described, for example, in Arbuck and Blaylock (1995), which is incorporated herein by reference.

It will be appreciated that use of the storage solution of the invention may be made in combination with any other anti-cancer regimen deemed appropriate for the patient. For example, the storage solution of the invention may be used in combination with cisplatin, edatrexate, L-buthionine sulfoxide, tiazofurin, gallium nitrate, doxorubicin, etoposide, or cyclo-

phosphamide, for example, or may be used in combination with radiation therapy. Further, while the preceding discussion describes the advantages of the vehicle of the invention in terms of utility with taxol, the invention contemplates use of the vehicle with other non-polar taxol/taxane derivatives, such as docetaxel, whether of synthetic or natural origin.

The following examples illustrate but are not intended in any way to limit the invention.

## Example 1

### Taxol Formulations

For the studies described below, two formulations, were prepared in the following proportions.

| | Formulation 1 | Formulation 2 |
|---|---|---|
| PEG 300 | 20 mL | 25 mL |
| Absolute Ethanol | 10 mL | 10 mL |
| Anhydrous citric acid | 100 mg | 100 mg |
| "CREMOPHOR EL" | 15 mL | 10 mL |
| "TWEEN 80" | 5 mL | 5 mL |
| Taxol | 300 mg | 300 mg |
| Final Volume: | 50 mL | 50 mL |

To prepare the above formulations, the PEG 300, citric acid and ethanol (EtOH) were mixed with a high speed mixer or stir bar until the citric acid was completely dissolved. If necessary, the mixture was heated to 50°C or sonicated to complete dissolution. To the mixture was then added "CREMOPHOR EL" and "TWEEN 80", and the resultant mixture was stirred for 30 minutes with a high speed mixer. The taxol was then added, and mixing was continued until the taxol was completely dissolved. The resulting solution was purged with dry nitrogen and filtered through a 0.22 micron filter ("MILLIPACK" 200). In both formulations, the final concentration of taxol was 6 mg/mL.

## Example 2

### Temperature Stability

Samples of Formulations 1 and 2 (200 $\mu$L each) were placed in 2 mL amber vials, which were then purged with nitrogen, stoppered using Teflon-coated rubber stoppers and sealed with aluminum seals. The vials were placed in an autoclave and heated under pressure at 250°F for 20 minutes. The samples were then diluted with HPLC-grade acetonitrile (1:20) and analyzed by HPLC on a Waters C8 Novapak column (8 mm I.D. × 10 cm, buffer A = 20% acetonitrile in water, 0.1% trifluoroacetic acid; buffer B = 80% acetonitrile in water,

0.1% trifluoroacetic acid; isocratic gradient at 45% B; detection at 230 nm). HPLC analysis showed no sign of degradation of the taxol.

Example 3

Comparative Long Term Stability of Formulations

Samples (200 μL each) of Formulations 1 and 2, and a formulation containing taxol (6 mg/mL) in a 1:1 mixture of "CREMOPHOR EL" and ethanol (Formulation 3), were placed in 2 mL amber vials which were then purged with nitrogen, sealed, and placed in a heat chamber at 37°C. Samples (50 μL) were withdrawn at 1, 3, 6 and 12 weeks, diluted with HPLC-grade acetonitrile (1:20) and analyzed by HPLC. The results were as follows:

| Time (wks) | Formulation, Percentage Taxol Remaining | | |
|---|---|---|---|
| | #1 | #2 | #3 |
| 1 | 100 | 100 | 100 |
| 6 | 98.8 | 98.8 | 98.7 |
| 12 | 98.7 | 98.8 | 97.8 |

Example 4

Stability of Taxol Formulations

Stock solutions in accordance with Formulations 1 and 2 were diluted 1:5, 1:10, 1:25 and 1:50 in normal saline (0.9% NaCl in water) to give taxol concentrations of 1.2, 0.6, 0.24, and 0.12 mg/mL, respectively. The solutions were checked at 1, 2, 4, 8, 24, and 48 hours for signs of precipitation or cloudiness.

All dilute solutions of Formulation 1 remained clear after 48 hours, showing no signs of cloudiness or precipitation. All dilute solutions of Formulation 2 were clear after 24 hours, but all showed some precipitation after 48 hours, with the 1:5 dilution of Formulation 2 showing the most precipitation.

Example 5

Comparative Toxicities of Taxol Formulations

A. Toxicity of Undiluted Samples. Samples of taxol Formulations 1, 2 and 3 were tested in undiluted form for acute toxicity in Balb/C mice. The samples were administered intravenously, over a range of administered volumes, to groups of 2 or 3 mice weighing 18-

20 grams. The mice were then monitored for signs of intolerance for 21 days after administration. Signs of intolerance included any one of the following: (1) significant weight loss (>20%), (2) piloerection, (3) prolonged prostration, and (4) death. The results are tabulated below, where MTD is the maximum tolerated dose expressed in units of mL/kg.

| Formulation | MTD (mL/kg) | Number of Mice |
|---|---|---|
| #1 | 5.0 | 2 |
| #2 | 5.0 | 3 |
| #3 | < 2.5 | 3 |

B. Toxicity Following Long Term Administration. Samples of Formulations 1, 2 and 3 were diluted 1:1 in normal saline and administered intravenously to Balb/C mice (18-20 grams in weight), 4 times a day for 5 days. The mice were monitored for signs of intolerance from the time administration was started until 21 days after administration had ceased. The maximum tolerated cumulative doses are tabulated below:

| Formulation | MTD, mL/kg | Number of mice |
|---|---|---|
| #1 | 10 | 5 |
| #2 | 10 | 5 |
| #3 | 5.0 | 5 |

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications may be made without departing from the invention.

IT IS CLAIMED:

1. A taxane storage solution for pharmaceutical use, comprising:

(a) a taxane compound in a pharmaceutically pure form,

(b) a polyoxyethylene sorbitan fatty acid monoester,

(c) polyethoxylated castor oil, and

(d) ethanol,

wherein the monoester and polyethoxylated castor oil are present in amounts effective to reduce the toxicity of the taxane compound relative to the toxicity observed when either the monoester or the polyethoxylated castor oil is used in the absence of the other, and the pH of the storage solution is between about 1 and about 8.

2. The solution of claim 1, additionally including a low molecular weight polyethylene glycol.

3. The solution of claim 1 or claim 2, additionally including a pharmaceutically acceptable acid, and wherein the pH of the solution is between about 4 and about 6.

4. The solution of claim 3, wherein the acid is anhydrous citric acid.

5. The solution of claim 1, comprising 4 mg/mL to 8 mg/mL taxane compound, 20 to 30% (v:v) polyethoxylated castor oil, 5 to 15% (v:v) polyoxyethylene (20) sorbitan mono-oleate, 15 to 30% (v:v) ethanol, and 40 to 60% (v:v) low molecular weight polyethylene glycol.

6. The solution of any of claims 1 to 5, wherein the taxane is taxol.

7. A method of preparing a taxane solution for intravenous administration, comprising:

providing a taxane storage solution in accordance with claim 1, and

diluting the storage solution with a diluent suitable for intravenous administration, to produce a dilute taxol solution.

8. The method of claim 7, wherein the storage solution additionally includes a low molecular weight polyethylene glycol.

9. The method of claim 7 or claim 8, wherein the storage solution additionally includes a pharmaceutically acceptable acid, and the pH of the storage solution is between about 4 and about 6.

10. The method of claim 9, wherein the acid is anhydrous citric acid.

11. The method of claim 7, wherein the taxol storage solution comprises 4 mg/mL to 8 mg/mL taxol, 20 to 30% (v:v) polyethoxylated castor oil, 5 to 15% (v:v) polyoxyethylene (20) sorbitan mono-oleate, 15 to 30% (v:v) ethanol, and 40 to 60% (v:v) low molecular weight polyethylene glycol.

12. The method of any of claims 7 to 11, wherein the taxane is taxol.

13. A method of treating cancer in a mammalian subject, comprising:

providing a taxane storage solution in accordance with any of claims 1 to 6,

diluting the storage solution with a diluent suitable for intravenous administration, to produce a dilute taxane solution, and

administering to the subject the dilute taxane solution in a pharmaceutically acceptable amount effective to inhibit growth of said cancer in the subject.

14. The method of claim 13, wherein the storage solution additionally including a low molecular weight polyethylene glycol.

15. The method of claim 13 or claim 14, wherein the storage solution additionally includes a pharmaceutically acceptable acid, and the pH is between about 4 and about 6.

16. The method of claim 15, wherein said acid is anhydrous citric acid.

17. The method of claim 13, wherein the storage solution comprises 4 mg/mL to 8 mg/mL taxol, 20 to 30% (v:v) polyethoxylated castor oil, 5 to 15% (v:v) polyoxyethylene

(20) sorbitan mono-oleate, 15 to 30% (v:v) ethanol, and 40 to 60 (v:v) low molecular weight polyethylene glycol.

18. The method of claim 17, wherein the pH is between about 4 and about 6.

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# INTERNATIONAL SEARCH REPORT

International application No.
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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 31/335; C07D 305/14
US CL : 514/449; 549/510, 511

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/449; 549/510, 511

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
search terms: taxane, sorbitan, castor, paclitaxel

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X, P | US 5,504,102 A (AGHARKAR et al.) 02 April 1996, see the entire document. | 1-5, 7-11 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 06 FEBRUARY 1997 | 26 MAR 1997 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer I W for<br>BA K. TRINH<br>Telephone No. (703) 308-1235 |

Form PCT/ISA/210 (second sheet)(July 1992)*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20187

**Box I Observations where certain claims were found unsearchable (Continuation f item 1 f first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6, 12-18
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark n Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.